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Applicability of diagnostic constructs for cognitive impairment in patients with type 2 diabetes mellitus

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ABSTRACT

Aims: Type 2 diabetes mellitus (T2DM) is associated with subtle cognitive changes, but also with more severe stages of cognitive dysfunction, including mild cognitive impairment (MCI) and dementia. For these severe stages, it is uncertain which domains are primarily affected and if all patients with impairment are captured by formal criteria for MCI or dementia.

Methods: Ninety-five patients with T2DM suspected of cognitive impairment, identified through screening in primary care, underwent neuropsychological examination assessing five different domains. MCI or dementia were diagnosed using formal criteria.

Results: Forty-seven participants (49%) had impairment on at least one domain, most often involving memory (30%), information processing speed (22%) and visuoperception and construction (22%). Of these 47 people, 29 (62%) had multi-domain impairment. Of the 47 participants with objective impairment, 36 (77%) met criteria for MCI, three (6%) for dementia and eight (17%) met neither diagnosis, mostly because these patients did not complain about acquired dysfunction.

Conclusions: This study shows that the clinical diagnostic evaluation of cognitive impairment in patients with T2DM should take into account that multiple domains can be affected and that not all patients with objective cognitive impairment fulfill criteria for MCI or dementia.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is associated with cognitive dysfunction. This includes subtle cognitive changes, also referred to as diabetes-associated cognitive decrements, as well as an increased risk of severe cognitive dysfunction, including mild cognitive impairment (MCI) and dementia [1,2]. It is well established that diabetes-associated cognitive decrements involve the domains memory, information processing speed, and attention and executive functioning [1,3]. It cannot be taken for granted, however, that for more severe stages of cognitive dysfunction the patterns of affected domains are the same. According to current insights, subtle diabetes-associated cognitive decrements and more severe cognitive dysfunction do not necessarily represent a continuum, as different age groups are affected, with different prognoses, and different underlying processes may be involved [4,5]. Thus far, it is uncertain which domains are primarily affected in patients with T2DM and severe cognitive dysfunction. In addition, it is unknown which proportion of patients with T2DM and objective cognitive impairment meet formal criteria for MCI or dementia. Identification of affected cognitive domains and evaluation of the applicability of diagnostic constructs such as MCI or dementia are important to establish an accurate diagnosis in patients with T2DM and cognitive impairment.

Accurate recognition and diagnosis of cognitive impairment is particularly important in patients with diabetes, because (unrecognized) cognitive impairment is associated with worse health and treatment outcomes [6,7]. Hence, recent guidelines recommend caregivers to be vigilant in detecting cognitive impairment in patient with diabetes [6,7].

In the present study, we investigated a population-based cohort of elderly people with T2DM suspected for cognitive impairment, identified through cognitive screening in a primary care setting. The aim was to assess which cognitive domains were primarily affected in patients with formal cognitive impairment. We also determined if all individuals with T2DM and cognitive impairment are captured by formal criteria for MCI and dementia.

2. Subjects, materials and methods

2.1. Study population

Patients were derived from the Cognitive Impairment in Diabetes (Cog-ID) study. The design and main results of the Cog-ID study have been described previously [8,9]. Briefly, the Cog-ID aimed to evaluate the ability of the Test Your Memory (TYM) and Self-Administered Gerocognitive Examination (SAGE) to detect undiagnosed cognitive impairment in people with T2DM in primary care, using a full evaluation at a memory clinic as reference standard. 228 people aged ≥70 years with T2DM were recruited from primary care. Exclusion criteria were: diagnosis of dementia, previous investigation at a memory clinic, and inability to write or read. At first patients filled out two self-administered cognitive tests, the Test Your Memory (TYM) and the Self-Administered Gerocognitive Examination (SAGE). The TYM is a self-administered test consisting of 10 sub-tasks, including orientation, ability to copy a sentence, semantic knowledge, calculation, verbal fluency, similarities, naming, visuospatial abilities, and recall of a copied sentence. The ability to complete the test without help represents an 11th task. The maximum score is 50 points. A score of ≤39 is suggestive of dementia [10]. The SAGE questionnaire is a self-administered test, which examines orientation, language, memory, executive function, calculation, abstraction and visuospatial abilities. The maximum score is 22 points. A score of ≤14 is suggestive of dementia [11]. The Cog-ID main study revealed that the TYM and SAGE are appropriate screening tools to detect undiagnosed cognitive impairment in patients with T2DM in primary care [9]. It has been previously established that the TYM and the SAGE measure a broader range of cognitive domains than the Mini-Mental Stage Examination (MMSE), and may be more sensitive in detecting cognitive impairment [10–12].

Secondly, a general practitioner, blinded to the test scores, performed a structured evaluation including the MMSE. The MMSE consists of 11 tasks including the domains orientation in time and space, registration of three words, concentration and calculation, word recall, language and visuospatial abilities. The maximum score is 30 points. A score of ≤24 points is suggestive of dementia [13]. Subsequently, patients suspected of cognitive impairment (i.e. screen positives; based on an abnormal score on either of the three cognitive tests or based on the general practitioner's clinical evaluation) were invited for evaluation at a memory clinic, as well as a random sample of patients not suspected of cognitive impairment (i.e. the screen negatives).

Of the 107 screen-positive participants, 95 underwent a standardized memory clinic work-up and were included in the present study. Of the twelve screen-positive participants that did not attend the memory clinic, four declined the memory clinic visit, three had comorbidities, two had personal circumstances, two found a memory clinic visit too burdensome, and one did not want to know the diagnosis at the memory clinic.

A random sample of screen-negative participants comprised 32 patients, who underwent the same work-up. Of these, 25 had no objective cognitive impairment at the memory clinic and served as a reference group for the present study. The seven other screen-negative participants proved to have cognitive impairment at the memory clinic, despite the negative screening, and were therefore not included in the reference group.

2.2. Memory clinic evaluation

The memory clinic evaluation included an interview of cognitive complaints, an MMSE, a detailed neuropsychological assessment and recording of education level. Education level was divided into seven categories (scored according to Verhage, 1964) according to the Dutch educational system (1: did not finish primary school, 2: finished primary school, 3: did not finish secondary school, 4: finished secondary school, low level, 5: finished secondary school, medium level, 6: finished secondary school, highest level, and/or college degree, 7: university degree) [14].

2.3. Cognitive assessment: conventional theory-based cognitive domain constructs

The neuropsychological workup included 16 tasks. Based on standard neuropsychological practice and cognitive theory, the tasks were divided into five conventional cognitive domains: memory, information processing speed, attention and executive functioning, visuoperception and construction, and working memory [15]. The domain memory was assessed by the Rey Auditory Verbal Learning Test - immediate recall, delayed recall and recognition [16], and the Rey-Osterrieth Complex Figure Test (ROCF) – delayed recall [17]. The domain information processing speed was assessed by the Digit Symbol-Coding (Wechsler Adult Intelligence Test, 3rd ed. (WAIS-III) [18], the Stroop Color-Word Test - 1 and 2 [19] and the trail-making test (TMT) A [20]. The domain visuoconstruction was assessed by the ROCF – copy [21] and the Judgment of Line Orientation (JLO) [22]. The domain attention and executive functioning was assessed by the letter fluency test - letter A and N [23], the category fluency - animal naming [23], the TMT B/A [20] and the Stroop Color Word Test 3/2 [19]. The domain working memory was assessed by the WAIS-III Digit span – sum of forward and backward [18]. We established whether the participants had impairment on one or more of these cognitive domains, compared to normative values. Impairment on a domain was defined as a score <5th percentile on formal Dutch normative values in ≥50% of the available tasks measuring that domain. The use of normative values enabled us to compare cognitive functioning of the diabetic participants with age, gender and education matched healthy subjects from the general population.

2.4. Cognitive assessment: data-driven principal axis factoring with re-clustering of tasks into factors

It might be that the processes that affect cognitive functioning in patients with T2DM lead to a pattern of task deficits that are not reflected in the aforementioned conventional domain division. In order to explore if other patterns of impairment would appear when test scores are re-clustered into factors based on the actual performance on tasks, we used a data-driven approach applying assumption-free principal axis factoring (PAF) [24,25]. PAF is a statistical approach used to identify latent variables, or factors, that explain the pattern of correlations within a set of observed independent variables. PAF assumes that the factors are correlated, as is the case with neuropsychological data. Variables for which Pearson correlation coefficients (i.e. continuous data) can be calculated are suitable for PAF. A correlation matrix is calculated of variables consisting of multiple correlation coefficients. Subsequently, factors are extracted from the correlation matrix. With PAF it is possible to identify what the factors represent conceptually. This method may unravel a specific clustering of task deficits specific for patients with T2DM.

For PAF, the normative values could not be used. Instead, we used the data of the reference group (i.e. 25 screen-negative participants with no objective cognitive impairment at the memory clinic) to calculate adjusted z-scores for each test of the screen-positive participants. Specifically, the raw cognitive test scores on all separate tasks of the screen-positive participants were adjusted for age, gender and level of education of the reference group. These adjusted scores were then standardized into z-scores, based on the means and standard deviations of the test scores of the reference group. The adjusted z-scores were entered into PAF. In addition, we assessed whether participants had impairment on the factors yielded by PAF. Impairment on a factor was defined as a score <5th percentile on normative values in ≥50% of the available tasks comprising that factor.

2.5. Medical history and biometric measurements

Patients underwent an interview on clinical history and a neurological examination. Blood pressure, body weight and length were measured. Non-fasting HbA1c and cholesterol levels were measured with standard laboratory testing. Retinopathy was defined as self-report or a physician diagnosis. Neuropathy was defined as a score ≥6 on a modified version of the Toronto Clinical Neuropathy Scoring System [26,27]. A patient was considered to have nephropathy in case of an estimated glomerular filtration rate <60 mL/min/1.73 m^2 [28]. Hypertension was defined as a systolic pressure >140 mm Hg or a diastolic pressure >90 mm Hg or use of antihypertensive drugs primarily for hypertension. Hypercholesterolemia was defined as non-fasting cholesterol >6.2 mmol/L or self-reported use of lipid lowering drugs. Clinical manifest atherosclerotic non-cerebral arterial disease was defined as a history of myocardial infarction or endovascular treatment of carotid, coronal or peripheral arterial disease.

2.6. Diagnosis

Clinical diagnoses were made at a multidisciplinary team-meeting involving a neuropsychologist and neurologist, who were blinded to the results of the primary care screening. MCI was diagnosed in patients as neither normal nor demented, with acquired cognitive complaints (reflecting a marked change in cognition as opposed to cognitive complaints that already have been present for many years) and with objective cognitive impairment on at least one conventional theory-based cognitive domain, but with preserved basic activities of daily living [29]. In case information processing speed was the only affected domain, this was not sufficient for a diagnosis of MCI. Dementia was diagnosed according to the Diagnostic and statistical manual of mental disorders-IV criteria [30].

2.7. Statistical analyses

Differences in patient characteristics between the three groups, i.e. screen-positive patients without objective cognitive impairment, screen-positive patients with objective cognitive impairment and the reference group (screen-negative participants without cognitive impairment at the memory clinic) were calculated with ANOVA for means, Kruskal-Wallis tests for non-parametric data and $\chi 2$ tests for proportions, with a two-sided alpha of 0.05. Post-hoc comparisons were performed using a single-sided alpha of 0.05. Differences between screen-positive participants and

Table 1 – Patient characteristics.

	Screen-positive T2DM patients without objective cognitive impairment n = 48	Screen-positive T2DM patients with objective cognitive impairment n = 47	Screen-negative T2DM patients without objective cognitive impairment n = 25 (reference group)	P-value
Demographics				
Gender,% men	29 (60)	26 (55)	15 (60)	0.87
Age, y	77.0 ± 4.5	77.2 ± 5.2	76.3 ± 4.7	0.73
Education[a]	4 (3–5)	4 (3–5)	5 (4–6)	**<0.001**[b]
MMSE	28 (27–30)	28 (25 – 29)	29 (29 – 30)	**<0.001**[c]
MMSE < 27[d]	9 (19)	18 (38)	0 (0)	**0.001**[e]
TYM ≤ 39[f]	27 (56)	29 (64)	0 (0)	**<0.001** [g]
SAGE ≤ 14 [h]	34 (72)	34 (79)	0 (0)	**<0.001**[i]
Diabetes associated factors				
Diabetes duration, y	8.8 ± 8.1	9.0 ± 8.2	6.0 ± 4.9	0.24
HbA1c level,% (mmol/mol)	6.7 ± 0.91 (50.1 ± 9.9)	6.8 ± 0.83 (51.2 ± 9.1)	6.5 ± 0.53 (47.7 ± 5.8)	0.31
Use of oral antidiabetic agents	39 (81)	35 (75)	22 (88)	0.38
Use of insulin	11 (23)	14 (30)	3 (12)	0.24
Diabetes associated complications				
Retinopathy[j]	2 (4)	7 (15)	4 (16)	0.16
Peripheral neuropathy[k]	21 (53)	22 (61)	10 (48)	0.58
Nephropathy[l]	22 (46)	22 (47)	6 (25)	0.17
Vascular risk factors				
BMI, kg/m^2	28.3 ± 3.9	29.5 ± 5.2	28.9 ± 4.2	0.46
Hypertension[m]	36 (77)	39 (83)	19 (76)	0.67
Hypercholesterolemia[n]	38 (79)	38 (81)	20 (80)	0.98
Smoking ever	32 (67)	31 (66)	14 (56)	0.63
Clinical manifest atherosclerotic non-cerebral arterial disease[o]	9 (19)	12 (26)	6 (24)	0.75
History of stroke[q]	5 (10)	13 (28)	2 (8)	**0.04**[r]

P-values highlighted in bold are statistically significant ($p < 0.05$).

Data are presented as mean ± SD, n (%) or median (interquartile range).

T2DM, type 2 diabetes; MCI, mild cognitive impairment; MMSE, mini-mental state examination; TYM, Test Your Memory; SAGE, Self-Administered Gerocognitive Examination; BMI, Body Mass Index.

[a] Seven categories (1: Did not finish primary school, 2: finished primary school, 3: did not finish secondary school, 4: finished secondary school, low level, 5: finished secondary school, medium level, 6: finished secondary school, highest level, and/or college degree, 7: university degree) [14].

[b] Post hoc tests revealed that screen-positive participants with and without objective cognitive impairment did not differ with regard to education. The reference group had the highest level of education compared to the screen-positive participants with and without objective cognitive impairment.

[c] Post hoc tests revealed that both screen-positive groups had a lower MMSE score than the reference group. Screen-positive participants with objective cognitive impairment had a lower MMSE score than the screen-positive participants without objective cognitive impairment.

[d] MMSE <27 is suggestive of cognitive impairment [41].

[e] Post-hoc tests revealed that screen-positive participants with objective cognitive impairment had significantly more frequent an MMSE <27 than screen-positive participants without objective cognitive impairment.

[f] TYM≤ 39 is suggestive of dementia [10].

[g] Post hoc tests revealed that screen-positive participants with and without objective cognitive impairment did not differ with regard to a TYM ≤39.

[h] SAGE ≤14 is suggestive of dementia [11].

[i] Post hoc tests revealed that screen-positive participants with and without objective cognitive impairment did not differ with regard to a SAGE ≤14.

[j] Defined as self-report or a physician diagnosis.

[k] Rated with the Toronto Clinical Neuropathy Scoring System (score ≥ 6 is indicative for neuropathy) [18,19].

[l] Defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2 [20].

[m] Defined as systolic pressure >140 mm Hg or a diastolic pressure >90 mm Hg or use of antihypertensive drugs primarily for hypertension.

[n] Defined as non-fasting cholesterol >6.2 mmol/L or self-reported use of lipid lowering drugs.

[o] Defined as history of myocardial infarction or endovascular treatment of carotid, coronal or peripheral arterial disease.

[q] Defined as a clinical history of stroke.

[r] Post hoc tests revealed that the screen-positive participants with objective cognitive impairment had a higher occurrence of stroke than the other two groups.

Table 2 – Screen-positive patients with T2DM: Division of tasks into conventional cognitive domains and factors and profiles of cognitive impairment.

A. Conventional cognitive domain constructs

	Memory	Information processing Speed	Visuo-perception and construction	Attention and executive functioning	Working memory	Single-domain impairment	Multi-domain impairment
Cognitive tasks	– RAVLT (immediate recall) – RAVLT (delayed recall) – RAVLT (recognition) – ROCF (delayed recall)	– Digit Symbol-Coding (WAIS-III) – Stroop Colour-Word Test - 1 – Stroop Colour-Word Test - 2 – TMT – A	– ROCF - copy – JLO	– Letter fluency (A) – Letter fluency (N) – Category fluency (animals) – TMT B/A – Stroop Colour Word Test 3/2	– Digit span (sum of forward and backward) (WAIS-III)		
Screen-positive patients (n = 95): Impairment on conventional cognitive domains[a,b]	28/94 (30%)	20/93 (22%)	20/92 (22%)	7/93 (8%)	10/93 (11%)	18/95 (19%)	29/95 (31%)

B. Assumption-free principal axis factoring: re-clustering of tasks into factors[c]

Factors –Principal axis factoring	Factor – "Memory"[d]	Factor – "Speed"[d]	Factor – "Visual"[d]	Factor – "Executive"[d]	Factor – "Fluency"[d]	Single-factor impairment	Multi-factor impairment
Cognitive tasks	– RAVLT (immediate recall) – RAVLT (delayed recall) – RAVLT (recognition)	– Digit Symbol-Coding (WAIS-III) – Stroop Colour-Word Test - 1 – Stroop Colour-Word Test - 2 – Letter fluency (A) – Letter fluency (N)	– ROCF - copy – ROCF (delayed recall)	– Letter fluency (N) – Category fluency (animals) – Digit span (sum of forward and backward) (WAIS-III)	– Letter fluency (A) – Letter fluency (N) – Category fluency (animals)		
Screen-positive patients (n = 95): Impairment on factors[a,e]	28/93 (30%)	12/95 (13%)	21/92 (23%)	9/94 (10%)	8/94 (9%)	16/95 (17%)	23/95 (24%)

RAVLT, Rey Auditory Verbal Learning Test; ROCF, Rey-Osterrieth Complex Figure; WAIS-III, Wechsler Adult Intelligence Test, 3rd ed; TMT, Trail Making Test; JLO: Judgement of Line Orientation.

[a] Total numbers of participants vary because some tasks were not administered in some subjects.

[b] Impairment on a conventional cognitive domain was defined as scores <5th percentile on normative values in at least 50% of the available tasks measuring that domain.

[c] For principal axis factoring, actual test scores of the screen-positive patients were compared with a reference group. This reference group consisted of all screen-negative patients with no cognitive impairment at the memory clinic (25 out of 32). See text for a detailed description.

[d] Each factor yielded by PAF was named, according to the cognitive domain it was interpreted to represent.

[e] Impairment on a factor was defined as scores <5th percentile on normative values in at least 50% of the available tasks comprising that factor.

the reference group in raw cognitive test scores and conventional domain scores (based on z-scores of the individual tests) were calculated using ANCOVA, with age, gender and level of education included as covariates. Regarding PAF, factor loadings >0.40 were considered relevant for interpreting the factor. Factors with eigenvalues >1 (a measure of explained variance) were considered for interpretation.

2.8. Ethics

The Cog-ID study was conducted according to the principles of the declaration of Helsinki and in accordance with the Dutch law on Medical Research Involving Human Subjects Act (WMO). This study was approved by the medical ethics committee of the University Medical Center Utrecht, the Netherlands. Written informed consent was obtained from all participants.

3. Results

Patient characteristics are presented in Table 1. All three groups were similar with regard to age and gender. The reference group had a higher level of education compared to the screen-positive participants with and without objective cognitive impairment. Both screen-positive groups had a lower MMSE score than the reference group. Screen-positive participants with objective cognitive impairment had a lower MMSE score than the screen-positive participants without objective cognitive impairment. Of note, 38% of patients with objective cognitive impairment screened positive on the MMSE, 64% on the TYM and 79% on the SAGE. More details on the diagnostic properties of these screening tests has been presented in the original Cog-ID paper [9]. By definition, none of the screen negative patients had a positive screening test. Diabetes associated factors and complications did not differ between the three groups. Although not significant, screen-positive participants with objective cognitive impairment had longer diabetes duration, higher HbA1c and more frequently used insulin than the other groups. The prevalence of stroke was higher in screen-positive participants with objective cognitive impairment, than in the other two groups ($P < 0.05$). Vascular risk factors did not differ significantly. A comparison of cognitive test scores of screen-positive participants and the reference group is presented in Supplementary Table 1A. Mean differences in domain z-scores between screen-positives and the reference group ranged from −0.26 to −1.36 (Supplementary Table 1B).

According to conventional diagnostic criteria, forty-seven screen-positive participants (49%) had impairment on one or more cognitive domains. Impairments were most often (70%) found in other domains than memory, in particular information processing speed and visuoperception and construction (Table 2). Memory was affected in one third of the screen-positive participants (Table 2). Twenty-nine screen-positive participants (31%) had multi-domain impairment (Table 2).

PAF yielded a multicomponent solution, consisting of six factors. Factor loadings of PAF are presented in Supplementary Table 2. Five factors could be interpreted as representing cognitive domains and were named memory, speed, visual, executive and fluency (Table 2). Indeed, the data-driven clustering of tasks into these five factors closely matched the division of tasks comprising the corresponding conventional domains (Table 2). Impairment on 'factors' was similar compared with impairment on conventional domains (Table 2). The sixth factor yielded no meaningful interpretation and was discarded. Trail-making test A and Stroop Colour Word Test 3/2 showed negligible factor loadings and were therefore not incorporated into a factor.

Of the 47 participants with objective impairment, 36 (77%) met criteria for MCI, three (6%) for dementia and eight (17%) met neither diagnosis, due to a lack of complaints of acquired dysfunction. Of the three patients with a clinical diagnosis of dementia, two met the criteria for Alzheimer's disease and one for vascular dementia.

4. Discussion

Patients with T2DM and objective cognitive impairment on neuropsychological assessment had a heterogeneous cognitive profile. All tested domains could be affected and one third of the patients had multi-domain impairment. Formal criteria for MCI and dementia only captured five out of six patients (83%) with T2DM and objective cognitive impairment, mostly because some patients had impairment in the absence of acquired cognitive complaints.

Patients participating in this study were recruited from the general elderly population. Previous population-based studies – not specifically in T2DM – compared occurrence of MCI subtypes, mostly comparing amnestic and non-amnestic MCI, and found variable results [31,32]. A systematic review which included nine population-based studies reported an incidence of amnestic MCI subtypes (single-domain and multi-domain) ranging from 9.9 to 40.6 per 1000 person-years, and an incidence of non-amnestic subtypes (single-domain and multi-domain) between 28 and 36.3 per 1000 person-years [33]. This is largely in line with our findings in patients with T2DM. If anything, the proportion of patients with non-amnestic MCI is even higher in T2DM. The non-amnestic MCI subtype is often associated with a vascular etiology of cognitive impairment [34,35]. Indeed, there is an association between T2DM and co-occurrence of other vascular risk factors as well as an increased risk for ischemic stroke [36]. This is in line with our study, where screen-positive participants with objective cognitive impairment had a higher prevalence of stroke.

Our study also shows that the domain constructs that are commonly used to establish cognitive impairment are appropriate in patients with T2DM, as PAF yielded no novel patterns of impairment, compared to conventional domain constructs. As noted, all cognitive domains could be affected. This has implications for both diagnosis and functional impact of cognitive impairment in T2DM. If the diagnosis is based on brief assessment tools rather than a full neuropsychological examination these tools should cover different domains. Of note, the MMSE even when a high threshold of <27 points was applied identified only 38% of the patients with objective cognitive impairment, which is likely due to the fact that it is a memory and orientation focussed test. In that respect,

the TYM and SAGE performed better, as reported previously [9]. Hence, if more elaborate testing then the brief self-administered SAGE and TYM tools is indicated, a test like the Montreal Cognitive assessment (MoCA) would be a good option, since it assesses a broader range of domains beyond memory [37]. With regard to functional impact, several of the commonly impaired cognitive domains in the patients with T2DM concern a decreased ability to efficiently process unstructured information, which would impact, among others, complex diabetes self-care activities [38,39]. This may lead to poor medication adherence and poor glycemic control, with an increased occurrence of hypoglycemic episodes and an increased frequency of hospital admissions [38].

One out of every six (17%) of our patients with objective cognitive impairment did not meet diagnostic criteria for MCI or dementia, mainly due to the absence of cognitive complaints, or because cognitive complaints had already been present for many years (i.e. could not be classified as acquired cognitive complaints). Nevertheless, such impairments may still affect diabetes management and are relevant to consider in patient management. Finally, we observed that 48 (50%) of the 95 screen-positive participants had no objective cognitive impairment at the memory clinic. This proportion of participants with a false-positive screen is similar to what is observed in studies on the accuracy of screening instruments for cognitive impairment in primary care [40].

The main strength of the present study is the detailed recording of cognitive functioning. Cognitive performance of all patients was evaluated against Dutch reference values, according to neuropsychological standards, to match diagnostic procedures in daily practice. Of note, level of education in the screen-positive patients was lower than in the reference group. This may have had some influence on the PAF. Yet, domain constructs as identified through PAF were very similar to the domains defined based on conventional criteria. A limitation is that the reference group for the PAF had a modest sample size. Of note, this limitation does not apply to the cognitive profiles in the upper panel of Table 2 as that is based on large Dutch databases of normative values. Another limitation that may affect external validity of the results is that the participants had relatively good glycemic control, few used insulin and the occurrence of diabetes associated complications was relatively low. Rates and features of cognitive impairment may be different in patients with worse control.

In conclusion, cognitive impairment in patients with T2DM can affect various domains and this should be taken into account in their assessment. Specifically, tests should also address non-amnestic deficits in patients with T2DM suspected for cognitive impairment. Moreover, one out of every six patients with T2DM and objective cognitive impairment does not meet diagnostic constructs for MCI or dementia. However, also in these patients cognitive impairments are relevant to address, as they may impact diabetes self-management and other aspects of socio-occupational functioning.

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Contributors

Onno Groeneveld (O.N.G.) wrote the first draft of the manuscript. Guy Rutten (G.E.H.M.), Paula Koekkoek (P.S.K.), Jaap Kappelle (L.J.K). and Geert Jan Biessels (G.J.B.) were substantial contributors in terms of study conception and design. O.N.G., Esther van den Berg (E.B.), P.S.K. and G.J.B. contributed substantially to the acquisition of data. All authors contributed substantially to the interpretation of the data. E.B., G.E.H.M., P.S.K., L.J.K. and G.J.B. revised the manuscript. All authors have approved the final version of the manuscript.

Conflict of interest

O.N.G., G.E.H.M.R., P.S.K., have no competing interests to declare. E.v.d.B. is a consultant for Boehringer Ingelheim. L.J.K. is a consultant for Boehringer Ingelheim. G.J.B. is a consultant for and receives research support from Boehringer Ingelheim, is a consultant for Takeda Pharmaceuticals, and has received speaker's fees from Eli Lily. Compensation for these activities is transferred to their employer, the UMC Utrecht.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.diabres.2018.05.025.

REFERENCES

[1] Koekkoek PS, Kappelle LJ, van den Berg E, Rutten GEHM, Biessels GJ. Cognitive function in patients with diabetes mellitus: Guidance for daily care. Lancet Neurol 2015;14(3):329–40.
[2] Cheng G, Huang C, Deng H, Wang H. Diabetes as a risk factor for dementia and mild cognitive impairment: A meta-analysis of longitudinal studies. Intern Med J 2012;42(5):484–91.
[3] Palta P, Schneider ALC, Biessels GJ, Touradji P, Hill-Briggs F. Magnitude of cognitive dysfunction in adults with type 2 diabetes: a meta-analysis of six cognitive domains and the most frequently reported neuropsychological tests within domains. J Int Neuropsychol Soc 2014;20(3):278–91.
[4] Biessels GJ, Strachan MWJ, Visseren FLJ, Kappelle LJ, Whitmer RA. Dementia and cognitive decline in type 2 diabetes and prediabetic stages: Towards targeted interventions. Lancet Diabetes Endocrinol 2014;2(3):246–55.
[5] Van Den Berg E, Reijmer YD, De Bresser J, Kessels RPC, Kappelle LJ, Biessels GJ. A 4 year follow-up study of cognitive functioning in patients with type 2 diabetes mellitus. Diabetologia 2010;53(1):58–65.
[6] Sinclair AJ, Hillson R, Bayer AJ, Burns A, Forbes A, Gadsby R, et al. Diabetes and dementia in older people: A best clinical practice statement by a multidisciplinary national expert working group. Diabet Med 2014;31(9):1024–31.

[7] American Diabetes Association. Older Adults: *Standards of Medical Care in Diabetes—2018*. Diabetes Care 2018;41 (Supplement 1):S119–25.
[8] Koekkoek PS, Janssen J, Kooistra M, van den Berg E, Kappelle LJ, Biessels GJ, et al. Cognitive impairment in diabetes: Rationale and design protocol of the cog-ID study. JMIR Res Protoc 2015;4(2):e69.
[9] Koekkoek P, Janssen J, Biesbroek JM, Groeneveld ON, van den Berg E, Kappelle LJ, et al. Case-finding for cognitive impairment with the test your memory and self-administered gerocognitive examination TYM and SAGE questionnaires in type 2 diabetes in primary care - the Cog-ID study. Diabet Med 2016;33:812–9.
[10] Brown J, Pengas G, Dawson K, Brown L.A, Clatworthy P. Self administered cognitive screening test (TYM) for detection of Alzheimer's disease: cross sectional study. Bmj. 2009;338: b2030–b2030.
[11] Scharre DW, Chang SI, Murden RA, Lamb J, Beversdorf DQ, Kataki M, et al. Self-administered gerocognitive examination (SAGE): A brief cognitive assessment instrument for mild cognitive impairment (MCI) and early dementia. Alzheimer Dis Assoc Disord 2010;24(1):64–71.
[12] Koekkoek PS, Rutten GEHM, Van Den Berg E, Van Sonsbeek S, Gorter KJ, Kappelle LJ, et al. The "test Your Memory" test performs better than the MMSE in a population without known cognitive dysfunction. J Neurol Sci 2013;328(1–2):92–7.
[13] Folstein MF, Folstein SEMP. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12(3):189–98.
[14] Verhage F. Intelligence and age (in Dutch). Gorcum V, editor. Assen; 1964.
[15] Lezak MD, Howieson DB, Bigler ED, Tranel D. Neuropsychological assessment. 5th ed. New York, NY: Oxford University Press; 2012.
[16] Van der Elst W, van Boxtel MPJ, van Breukelen GJP. Rey's verbal learning test: Normative data for, healthy participants aged 24–81 years and the influence of age, sex, education, and mode of presentation. J Int Neuropsychol Soc 1855;2005:290–302.
[17] Rey A. L'examen psychologique dans les cas d'encefalopathie traumatique: Les problemes. Arch Psychol (Geneve). 1941;28 (286–340).
[18] Moses J. Neuropsychological information in the Wechsler adult intelligence scale—revised. Arch Clin Neuropsychol 1997;12(2):97–109.
[19] Stroop J. Studies of interference in serial verbal reactions. J Exp Psych Gen 1935;121(1):15–23.
[20] Corrigan JDHN. Relationships between parts A and B of the trail making test. J Clin Psychol 1987;43(4):402–9.
[21] Pa O Le. test du copie d'une figure complexe. Arch Psychol 1944;30:206–356.
[22] Benton AL. Contributions to neuropsychological assessment. Oxford: Oxford University Press; 1983.
[23] Deelman BG, Liebrand WB, Koning-Haanstra M, van der BW. Measurements of aphasic disorders. A brief description of the SAN-battery. Gerontologie 1980;11(1):17–21.
[24] Gorsuch RL. Factor analysis. 2nd ed. Lawrence Erlbaum Associates; 1983.
[25] Manual IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp; 2013.
[26] Bril V, Perkins BA. Validation of the Toronto clinical scoring system for diabetic polyneuropathy. Diabetes Care 2002;25 (11):2048–52.
[27] Manschot SM, Biessels GJ, De Valk H, Algra A, Rutten GEHM, Van Der Grond J, et al. Metabolic and vascular determinants of impaired cognitive performance and abnormalities on brain magnetic resonance imaging in patients with type 2 diabetes. Diabetologia 2007;50(11):2388–97.
[28] American Diabetes Association. Standards of medical care in diabetes - 2017. J Clin Appl Res Educ 2017;40(January):1–142.
[29] Winblad B, Palmer KKM. Mild cognitive impairment– beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med 2004;256(3):240–6.
[30] Diagnostic and statistical manual of mental disorders: DSM-IV. Washington, DC: American Psychiatric Association; 2000.
[31] Roberts RO, Geda YE, Knopman DS, Cha RH, Pankratz VS, Boeve BF, et al. The incidence of MCI differs by subtype and is higher in men: The Mayo Clinic study of aging. Neurology 2012;78(5):342–51.
[32] Brodaty H, Heffernan M, Kochan N.A, Draper B, Trollor JN, Reppermund S, et al. Mild cognitive impairment in a community sample: The Sydney Memory and Ageing Study. Alzheimer's Dement 2013;9(3):310–317.e1.
[33] Luck T, Luppa M, Briel S, Riedel-Heller SG. Incidence of mild cognitive impairment: A systematic review. Dement Geriatr Cogn Disord 2010;29(2):164–75.
[34] Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, et al. Seminar Mild cognitive impairment. Lancet 2006;367(April 15):1262–70.
[35] Petersen RC, Caracciolo B, Brayne C, Gauthier S, Jelic V, Fratiglioni L. Mild cognitive impairment: A concept in evolution. J Intern Med 2014;275(3):214–28.
[36] Luitse MJA, Biessels GJ, Rutten GEHM, Kappelle LJ. Diabetes, hyperglycaemia, and acute ischaemic stroke. Lancet Neurol 2012;11(3):261–71.
[37] Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53(4):695–9.
[38] Munshi MN. Cognitive dysfunction in older adults with diabetes: What a clinician needs to know. Diabetes Care 2017;40(4):461–7.
[39] Brands AMA, Van Den Berg E, Manschot SM, Biessels GJ, Kappelle LJ, De Haan Edward H, et al. A detailed profile of cognitive dysfunction and its relation to psychological distress in patients with type 2 diabetes mellitus. J Int Neuropsychol Soc 2007;13(2):288–97.
[40] Brodaty H, Low L-F, Gibson L, Burns K. What is the best dementia screening instrument for general practitioners to use? Am J Geriatr Psychiatry 2006;14(May):391–400.
[41] Crum RM, Anthony JC, Bassett SSFM. Population-based norms for the Mini-Mental State Examination by age and educational level. JAMA 1993;269(18):2386–91.